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ITC

CERTIFICATION

1. I, the undersigned Lawrence B. Hanlon, do hereby avow and declare that I am conversant with the English and Spanish languages and am a competent translator of Spanish into English.

2. I do further declare that the attached translation is, to the best of my knowledge and belief, a true, correct, and complete translation into English of the original Spanish-language Patent Application No. **20021826** entitled **Novel derivatives of 2,4-dihydroxybenzoic acid**, which Spanish patent application is also attached herewith.

3. Furthermore, I hereby declare that the statements made above are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Lawrence B. Hanlon

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12/16/2008

Date

Translation of Spanish Application P 200201826, filed July 18, 2002

Novel derivatives of 2,4-dihydroxybenzoic acid.

Field of the invention.

The present invention relates to a novel series of derivatives of 2,4-dihydroxybenzoic acid, as well as to a process for their preparation, to the pharmaceutical compositions containing them and to their use for the manufacture of medicaments, particularly for the treatment or prevention of psoriasis and other immune diseases.

Description of the prior art.

Psoriasis is a chronic inflammatory disease of the skin that affects as much as 2% of the world's population. Patients exhibit epidermal proliferation leading to erythema, scaling, and thickening of the skin, which can range from mild to severe. The disease is characterized by the hyperplasia of the skin and the infiltration of T-lymphocytes, monocytes and neutrophils into the epidermis.

Although there are various topical and systemic symptomatic treatments for psoriasis, such as UV light, glucocorticoids, vitamin D analogs, retinoids, tazarotene, methotrexate and cyclosporine, there is no effective therapy to cure the disease. Furthermore, some of the current treatments are aggressive and cause important side effects.

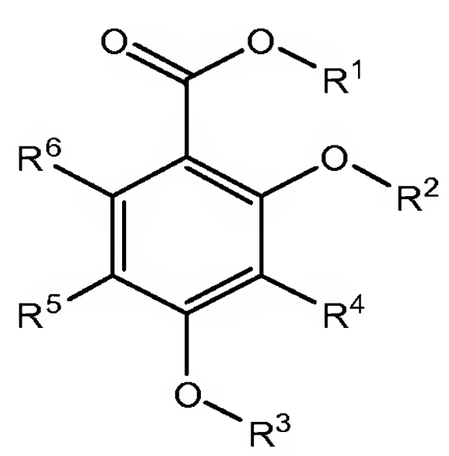
Thus, there presently exists a need to find novel drugs useful for the treatment of psoriasis. This problem is solved by the derivatives of 2,4-dihydroxybenzoic acid of formula **I** of the present invention.

Some derivatives of 2,4-dihydroxybenzoic acid structurally close to the compounds of the invention have been disclosed in the literature. In particular, in J. Mu et al, C*olloids and surfaces, A: Physicochemical and Engineering Aspects*, **2001**, *181*, 303-313 the compounds ethyl 2-hydroxy-4-(3,3,4,4,5,5,6,6,6-nonafluorohexyloxy)benzoate, ethyl 2-hydroxy-4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyloxy)benzoate and ethyl 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyloxy)-2-hydroxybenzoate are disclosed. These compounds are useful as intermediates in the preparation of liquid crystals. No therapeutic application has been described for these compounds. In R. Arnold-Stanton and D. M. Lemal, *J. Org.Chem.* **1991**, *56*, 151-157 the compound methyl 2,6-dihydroxy-4-(1,1,2,2-tetrafluoroethoxy)benzoate is described as a by-product in a reaction of

1,3,5-trihydroxybenzene. No therapeutic application has been described for this compound. Finally, in I.R. Hardcastle et al, *Tetrahedron Letters* **2001**, *42(7)*, 1363-1365 the compound 2,3,5-trifluoro-4-(3-fluoropropoxy)-6-hydroxybenzoic acid is disclosed as a potential farnesyltransferase inhibitor, although as mentioned in said article, this compound was inactive; accordingly, no therapeutic application has been described for this compound.

Description of the invention.

One aspect of the present invention relates to the novel compounds of general formula **I**:



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

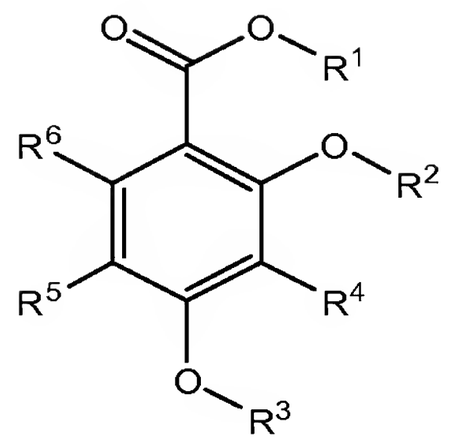
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

with the proviso that when R^1 represents methyl, R^2 represents hydrogen, R^3 represents 1,1,2,2-tetrafluoroethyl and R^4 and R^5 represent hydrogen then R^6 cannot be hydroxy, and with the further proviso that when R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents 3-fluoropropyl then R^4, R^5 and R^6 together cannot simultaneously represent fluoro.

A further aspect of the invention relates to a compound of general formula **I**:



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

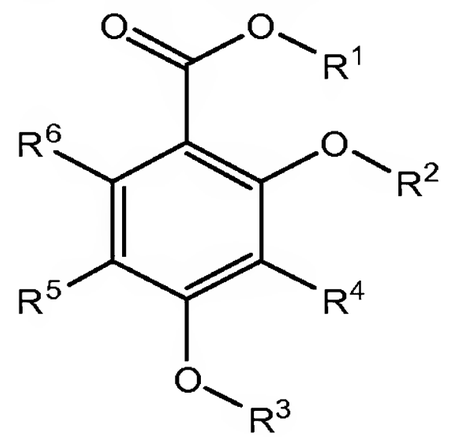
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

for use as an active pharmaceutical ingredient.

A further aspect of the invention relates to a compound of general formula **I**:



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

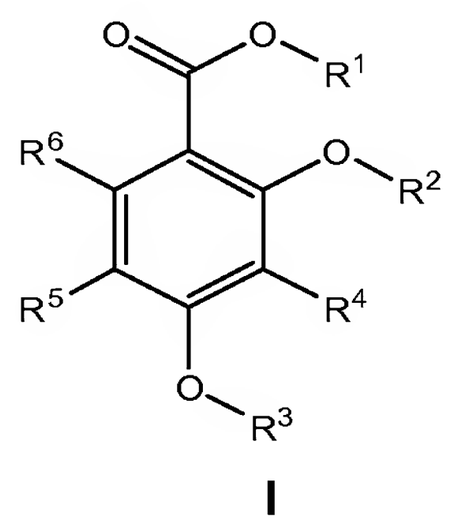
for use in a method of treatment of the human or animal body.

The present invention also relates to the salts of the compounds of the invention as well as to their solvates and prodrugs. The term prodrug refers to any precursor of a compound of formula **I** which is able to be transformed *in vivo* into a compound of formula **I**.

Some compounds of formula **I** can have chiral centres, which can give rise to various stereoisomers. The present invention relates to each one of the individual stereoisomers as well as to their mixtures.

The compounds of formula **I** disclosed in the present invention have shown very good activity in animal models for psoriasis. Likewise, these compounds have shown good activity in pharmacological models of immunomodulation, for example they have been proved to inhibit T-lymphocyte proliferation, and therefore they could be useful for the treatment or prevention of other immune diseases as well. Furthermore, the compounds of the present invention show a good tolerance profile.

Therefore, a further aspect of the present invention relates to the pharmaceutical compositions which comprise an effective amount of a compound of formula **I**



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

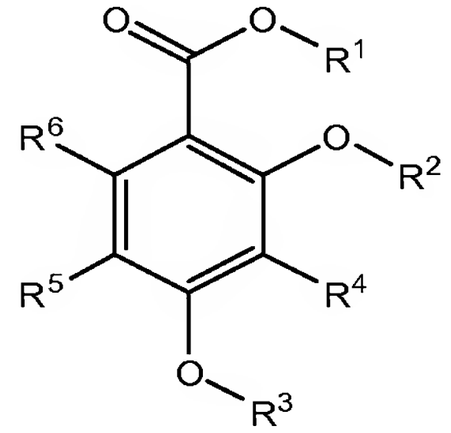
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a pharmaceutically acceptable salt, solvate or prodrug thereof and one or more pharmaceutically acceptable excipients.

A further aspect of the present invention relates to the use of a compound of formula I



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

R^7 and R^{10} independently represent C_{1-4} alkyl;

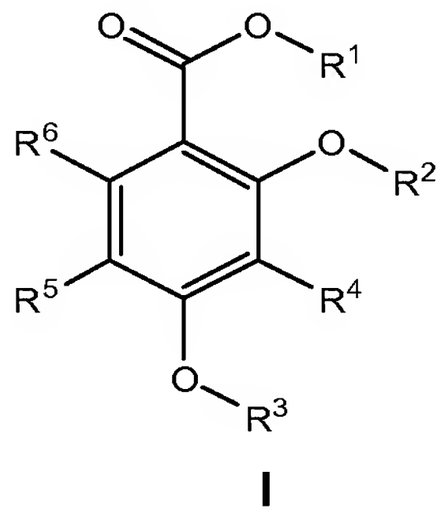
R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of immune diseases. In a preferred embodiment, such diseases are psoriasis, other skin diseases such as atopic dermatitis, contact dermatitis, lichen planus, dermatomyositis, scleroderma, erythema multiforme, urticaria and pemphigus, inflammatory bowel disease including Crohn's disease and ulcerative colitis, rheumatoid arthritis and other arthritic diseases such as gouty arthritis, psoriatic arthritis, juvenile arthritis and ankylosing spondylitis, multiple sclerosis and other autoimmune neuropathies, diabetes, transplant rejection, graft-versus-host disease, lupus erythematosus,

vasculitis, Sjögren's syndrome, Guillain-Barré syndrome, glomerulonephritis, respiratory diseases such as allergic rhinitis or asthma, and neoplasias with immune system cell proliferation.

A further aspect of the present invention relates to a process for preparing a compound of formula **I**,



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

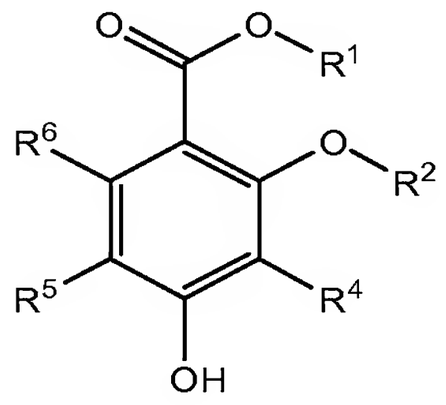
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

which comprises:

(a) reacting a phenol of formula **II**



II

wherein R^1, R^2, R^4, R^5 and R^6 have the meaning described above, with an alkylating agent of formula $G\text{-}R^3$ (**III**), wherein R^3 has the meaning described

above and G represents a good leaving group; or

(b) converting, in one or more steps, a compound of formula **I** into another compound of formula **I**; and

(c) if desired, after the above steps and when R^1 and/or R^2 represent hydrogen, reacting a compound of formula **I** with a base, to obtain the corresponding addition salt.

In the above definitions, and unless otherwise stated, the term C_{1-n} alkyl, as a group or part of a group, means a lineal or branched alkyl group containing from 1 to n carbon atoms. When n is 4, it includes the groups methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl. When n is 5, it includes in addition the groups pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-ethylpropyl, 2-ethylpropyl and 1,2-dimethylpropyl.

A C_{2-5} alkenyl group means a lineal or branched alkyl group containing from 2 to 5 carbon atoms and containing one or more double bonds.

A C_{2-5} alkynyl group means a lineal or branched alkyl group containing from 2 to 5 carbon atoms and containing one or more triple bonds.

A C_{1-4} alkoxy group means a group of formula "C_{1-4} alkyl-O-" and it includes the groups methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, and *tert*-butoxy.

The term halogen or its abbreviation halo means fluoro, chloro, bromo or iodo.

A C_{1-4} haloalkyl group means a group resulting from the replacement of one or more hydrogen atoms of a C_{1-4} alkyl group with one or more halogen atoms (that is, fluoro, chloro, bromo or iodo), which can be the same or different. Examples include, among others, the groups trifluoromethyl, fluoromethyl, 1-chloroethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1-bromoethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 4-fluorobutyl, 4-chlorobutyl and nonafluorobutyl.

A C_{1-4} haloalkoxy group means a group resulting from the replacement of one or more hydrogen atoms of a C_{1-4} alkoxy group with one or more halogen atoms (that is, fluoro, chloro, bromo or iodo), which can be the same or different. Examples include, among others, the groups trifluoromethoxy, fluoromethoxy, 1-

chloroethoxy, 2-chloroethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 1-bromoethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 3-fluoropropoxy, 3-chloropropoxy, 3,3,3-trifluoropropoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 4-fluorobutoxy, 4-chlorobutoxy and nonafluorobutoxy.

A C_{1-5} fluoroalkyl group means a C_{1-5} alkyl group, as defined above, wherein one or more hydrogen atoms are replaced with one or more fluorine atoms, including the possibility that all the hydrogen atoms are replaced with fluorine atoms. Examples include, among others, the groups trifluoromethyl, fluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 4-fluorobutyl, 4,4,4-trifluorobutyl, 3,3,4,4,4-pentafluorobutyl, nonafluorobutyl and 5-fluoropentyl. A C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group represents a C_{2-5} alkenyl or a C_{2-5} alkynyl group, respectively, wherein one or more hydrogen atoms are replaced with one or more fluorine atoms, including the possibility that all the hydrogen atoms are replaced with fluorine atoms. Examples of these include the corresponding unsaturated radicals of the groups cited as examples with respect to a C_{1-5} fluoroalkyl group, for instance a 2,3,3-trifluoropropen-2-yl group.

Although the present invention includes all the compounds mentioned above, those compounds of formula **I** wherein the R^1 group represents hydrogen are preferred.

Also preferred are those compounds of formula **I** wherein the R^2 group represents hydrogen or acetyl (that is, a $-C(=O)CH_3$ group).

Also preferred are those compounds of formula **I** wherein R^3 represents a C_{1-5} fluoroalkyl group, those compounds of formula **I** wherein R^3 represents a C_{1-3} fluoroalkyl group being more preferred. A particularly preferred class of compounds are those compounds of formula **I** wherein R^3 represents a 2,2,3,3,3-pentafluoropropyl group.

Also preferred are those compounds of formula **I** wherein R^4, R^5 and R^6 represent hydrogen.

Accordingly, a preferred embodiment of the present invention are the compounds of formula **I** wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or -C(=O)R^7;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 represent hydrogen; and

R^7 represents C_{1-4} alkyl;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula **I** wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or -C(=O)R^7;

R^3 represents a C_{1-5} fluoroalkyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, -NR^8R^9, -$S(O)_xR^{10}$ or -C(=O)R^{11};

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

with the proviso that when R^1 represents methyl, R^2 represents hydrogen, R^3 represents 1,1,2,2-tetrafluoroethyl and R^4 and R^5 represent hydrogen then R^6 cannot be hydroxy, and with the further proviso that when R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents 3-fluoropropyl then R^4, R^5 and R^6 together cannot simultaneously represent fluoro;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula **I** wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or -C(=O)R^7;

R^3 represents C_{1-5} fluoroalkyl;

R^4, R^5 and R^6 represent hydrogen; and

R^7 represents C_{1-4} alkyl;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula **I** wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or -C(=O)R^7;

R^3 represents a C_{1-3} fluoroalkyl, C_{2-3} fluoroalkenyl or C_{2-3} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

with the proviso that when R^1 represents methyl, R^2 represents hydrogen, R^3 represents 1,1,2,2-tetrafluoroethyl and R^4 and R^5 represent hydrogen then R^6 cannot be hydroxy, and with the further proviso that when R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents 3-fluoropropyl then R^4, R^5 and R^6 together cannot simultaneously represent fluoro;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula I wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-3} fluoroalkyl, C_{2-3} fluoroalkenyl or C_{2-3} fluoroalkynyl group;

R^4, R^5 and R^6 represent hydrogen; and

R^7 represents C_{1-4} alkyl;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula I wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-3} fluoroalkyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

with the proviso that when R^1 represents methyl, R^2 represents hydrogen, R^3 represents 1,1,2,2-tetrafluoroethyl and R^4 and R^5 represent hydrogen then R^6

cannot be hydroxy, and with the further proviso that when R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents 3-fluoropropyl then R^4, R^5 and R^6 together cannot simultaneously represent fluoro;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula I wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-3} fluoroalkyl group;

R^4, R^5 and R^6 represent hydrogen; and

R^7 represents C_{1-4} alkyl;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula I wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a 2,2,3,3,3-pentafluoropropyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

and the salts, solvates and prodrugs thereof.

Another preferred embodiment of the present invention are the compounds of formula I wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a 2,2,3,3,3-pentafluoropropyl group;

R^4, R^5 and R^6 represent hydrogen; and

R^7 represents C_{1-4} alkyl;

and the salts, solvates and prodrugs thereof.

In a particularly preferred embodiment of the present invention, R^1, R^2, R^4, R^5 and R^6 represent hydrogen and R^3 represents 2,2,3,3,3-pentafluoropropyl, that

is, the compound of formula **I** is 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid and the salts, solvates and prodrugs thereof.

In another particularly preferred embodiment of the present invention, R^1, R^4, R^5 and R^6 represent hydrogen, R^2 represents acetyl and R^3 represents 2,2,3,3,3-pentafluoropropyl, that is, the compound of formula **I** is 2-acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid and the salts, solvates and prodrugs thereof.

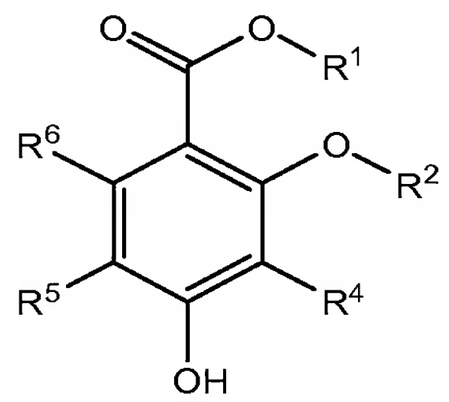
The compounds of the present invention may contain an acidic proton and, consequently, they can form salts with organic as well as inorganic bases, which are also included in the present invention. There is no limitation on the nature of these salts, provided that when used for therapeutic purposes they are phramaceutically acceptable. Examples of said salts include salts formed with pharmaceutically acceptable amines such as ammonia, alkylamines, hydroxyalkylamines, lysine, arginine, *N*-methylglucamine, procaine and the like, and salts formed with inorganic cations such as sodium, potassium, calcium, magnesium, lithium, aluminum, zinc, etc. The salts can be prepared by treatment of a compound of formula **I** with a sufficient amount of the desired base to give the salt in a conventional manner. The compounds of formula **I** and their salts differ in certain physical properties, such as solubility, but they are equivalent for the purposes of the invention.

Some compounds of the present invention can exist in solvated form, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated form for the purposes of the invention.

Some compounds of the present invention can exist as various diastereoisomers and/or optical isomers. Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. The optical isomers can be resolved using conventional techniques of optical resolution, to give the optically pure isomers. This resolution can be performed upon any chiral synthetic intermediates or upon the products of general formula **I**. The optically pure isomers can also be individually obtained using enantiospecific synthesis. The present invention covers both the individual isomers and the mixtures (for example racemic mixtures), whether obtained by synthesis or by physically mixing them up.

The present invention also provides a process for preparing the compounds of formula **I**. As it will be obvious to a person skilled in the art, the precise method used for the preparation of a given compound can vary depending on its chemical structure. Furthermore, in some of the processes that are detailed below it may be necessary or appropriate to protect the reactive or labile groups using conventional protecting groups. Both the nature of said protecting groups and the processes for their introduction and removal are well known and belong to the state of the art (see for example Greene T.W. and Wuts P.G.M., "Protective Groups in Organic Synthesis", 3rd Edition, John Wiley & Sons, 1999). For example, carboxyl groups can be protected as C_{1-4} alkyl esters, like methyl, ethyl or *tert*-butyl ester, or as arylC_{1-4} alkyl esters, like benzyl ester. Given a compound with a protecting group, a subsequent deprotection step will be necessary, which can be performed under standard conditions in organic synthesis, as described in the reference mentioned above.

The compounds of formula **I** can be obtained in general by alkylation of a phenol of formula **II**

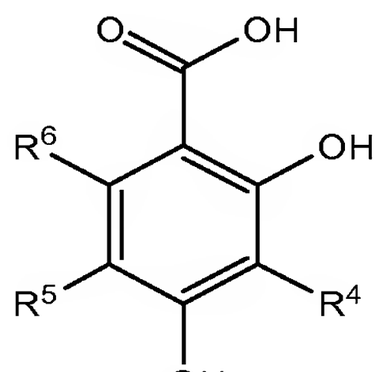


II

wherein R^1, R^2, R^4, R^5 and R^6 have the meaning described above, with an alkylating agent of formula G-R^3 (**III**), wherein R^3 has the meaning described above and G represents a good leaving group such as a halogen atom, for example chloro, bromo or iodo, or an alkyl-, haloalkyl- or arylsulfonate, for example mesylate, tosylate, 2,4,6-trimethylbenzenesulfonate or trifluoromethanesulfonate. This reaction is carried out in the presence of a suitable base for the deprotonation of the phenol, such as sodium, potassium or cesium carbonate, sodium or potassium hydroxide, sodium hydride, sodium or potassium *tert*-butoxide, or *n*-butyllithium, in the presence of a suitable solvent. Examples of suitable solvents include, among others, dimethyl sulfoxide, tetrahydrofuran, tetrahydrofuran-hexamethylphosphoramide mixtures and substituted amides such as for example dimethylformamide, dimethylacetamide and *N*-methyl-2-

pyrrolidinone. The reaction is carried out at a temperature comprised between 0 °C and the temperature of the boiling point of the solvent.

Alternatively, when in a compound of formula **II** R^1 and R^2 represent hydrogen, that is when it is a compound of formula **IIa**



IIa

(**II**, $R^1 = R^2 = H$)

the reaction can be also carried out under conditions that include the additional presence of a Lewis acid in the reaction medium. The process comprises the treatment of a compound of formula **IIa** in deprotonated form with said Lewis acid and subsequent addition of the alkylating agent in the reaction medium. Examples of suitable Lewis acids to carry out the reaction include, among others, a trialkylborate such as trimethylborate or triethylborate, metallic halides such as iron(III) chloride, magnesium bromide or zinc bromide, and trimethylsilyl chloride.

Alternatively, the compounds of the present invention can be also obtained by interconversion from another compound of formula **I**, in one or more steps, using standard conditions in organic chemistry.

For example, a R^1 group can be converted into another R^1 group, by conversion of a carboxylic acid into an ester. Such esterification can be carried out under standard conditions for the esterification of carboxylic acids, well-known for a skilled person in the art. Thus, for example, a compound of formula **I** as a carboxylic acid ($R^1 = H$) can be reacted with an alcohol of formula HO-R^1 (**IV**), wherein R^1 represents C_{1-4} alkyl, in the presence of a catalytic amount of a mineral acid such as for example sulfuric acid. Furthermore, a reactive derivative of said acid, such as an acyl halide, can be reacted with an alcohol of formula **IV**, in the presence of a weak base such as triethylamine or diisopropylethylamine. Alternatively, the carboxylic acid can be activated *in situ* using a suitable activating agent such as a carbodiimide, for example *N,N'*-dicyclohexylcarbodiimide or *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide, in the presence of a base such as

dimethylaminopyridine, triethylamine or diisopropylethylamine, and in the presence of a suitable solvent such as a halogenated hydrocarbon, for example dichloromethane or chloroform, or a substituted amide such as dimethylformamide.

Furthermore, the group R^2 can be converted into another group R^2 by transformation of a group -OH (R^2 = H) into a group -OC(=O)R^7 (R^2 = -C(=O)R^7). Said reaction can be carried out under standard conditions for the formation of ester bonds already mentioned before, preferably by reacting a compound of formula **I** wherein R^2 represents hydrogen with an anhydride of formula $[R^7C(=O)]_2O$, or with the corresponding acyl halide, in the presence of a suitable base. Suitable bases to carry out the reaction include pyridine or triethylamine or diisopropylethylamine in the presence of a suitable solvent such as a halogenated solvent, for example chloroform or dichloromethane.

Likewise, the compounds of formula **I** wherein R^1 represents C_{1-4} alkyl and/or wherein R^2 represents -C(=O)R^7 can be converted into other compounds of formula **I** wherein R^1 and/or R^2 represent hydrogen by hydrolysis of the corresponding ester bonds. The hydrolysis of said function can be carried out in the presence of a base such as potassium hydroxide or lithium hydroxide, in the presence of a suitable solvent such as a polar solvent, for example methanol, ethanol, tetrahydrofuran, methanol-water mixtures, ethanol-water mixtures or tetrahydrofuran-water mixtures, or an apolar solvent such as benzene in the presence of a crown ether, for example 18-C-6.

The phenols of formula **II** and the alkylating agents of formula **III** used for the preparation of compounds of formula **I** are commercially available, widely described in the literature or can be prepared starting from other commercially available compounds using standard transformations in organic chemistry, well-known to those skilled in the art.

Thus, for example, certain starting phenols of formula **II** which are not commercially available can be obtained by esterification and/or acylation of 2,4-dihydroxybenzoic acid, which is commercially available. These reactions are carried out according to the processes described before for the esterification and acylation of the compounds of formula **I**.

The alkylating agents of formula **III** can be commercially available, or when the leaving group G is an alkylsulfonate, haloalkylsulfonate or arylsulfonate they

can be obtained by reaction of an anhydride of the corresponding alkylsulfonic, haloalkylsulfonic or arylsulfonic acid with an alcohol of formula HO-R^3 (**V**), wherein R^3 has the meaning described above. Furthermore, they can also be obtained by reaction of the chloride of the corresponding alkyl-, haloalkyl- or arylsulfonic acid with said alcohols, in the presence of a base such as pyridine or diisopropylethylamine or triethylamine in the presence of a suitable solvent such as for example a halogenated hydrocarbon, such as dichloromethane or chloroform.

Likewise, alcohols of formula **V** can be commercially available or can be obtained from other commercially available compounds through standard transformations in organic chemistry, widely known for a skilled person in the art.

Finally, the salts of the compounds of formula **I** can be prepared by conventional methods, for example by treatment with a base such as sodium hydroxide or potassium hydroxide.

As mentioned above, the compounds of formula **I** show immunomodulating activity and therefore they are useful for the treatment or prevention of immune diseases. Examples of immune diseases which can be treated with the compounds of the invention include, among others, psoriasis, other skin diseases such as atopic dermatitis, contact dermatitis, lichen planus, dermatomyositis, scleroderma, erythema multiforme, urticaria and pemphigus, inflammatory bowel disease including Crohn's disease and ulcerative colitis, rheumatoid arthritis and other arthritic diseases such as gouty arthritis, psoriatic arthritis, juvenile arthritis and ankylosing spondylitis, multiple sclerosis and other autoimmune neuropathies, diabetes, transplant rejection, graft-versus-host disease, lupus erythematosus, vasculitis, Sjögren's syndrome, Guillain-Barré syndrome, glomerulonephritis, respiratory diseases such as allergic rhinitis or asthma, and neoplasias with proliferation of immune cells.

According to the activity of the products herein described, the present invention also relates to compositions which contain a compound of the present invention (or a pharmaceutically acceptable salt, solvate or prodrug thereof), together with an excipient or other auxiliary agents if necessary.

The compounds of the present invention show activity whether topically or systemically administered. Therefore, it should be possible to use any administration route for these products, for example topical, oral, parenteral or

rectal administration.

Formulations for topical administration of the product include creams, ointments, lotions, gels, powders, solutions and patches wherein the compound is dispersed or dissolved in suitable excipients, which in addition can facilitate its topical absorption such as diisopropyl myristate or diisopropyl adipate, octyldodecanol, polyethylene glycols and diethylene glycol monoethyl ether, among others.

The compound can be incorporated in ointments using a hydrophilic oily base such as for example polyethylene glycols or a hydrophobic oily base such as for example paraffin or liquid vaseline with polyethylene.

Emulsion formulations such as creams and lotions comprise an oily phase (5-40 %), an aqueous phase and an emulgent. For the oily phase it should be possible to use any excipient commonly-used in this type of formulations. The compound will be incorporated into the aqueous phase or into the oily phase depending on the excipient or excipients used to dissolve or disperse it. The choice of the emulgent will be conditioned by the type of emulsion: if an external aqueous phase (o/w emulsion) is used, an emulgent such as for example cetomacrogol or glycol stearate, among others, can be used, while if an external oily phase is used (w/o emulsion) an emulgent such as sorbitan tristearate or sorbitan monoisostearate, among others, can be used. Depending on the resulting viscosity, the pharmaceutical form will be a cream (semisolid consistency) or a lotion (liquid consistency).

Furthermore, the compound can be incorporated into a gel, matrix of a hydrophilic colloid such as for example carbomer.

All these topical compositions can additionally contain auxiliary excipients such as emolients, buffers, preservatives, antioxidants and perfuming agents.

Furthermore, the compound can also be presented for topical application in vectorized form using liposomes, nanoemulsions or nanocapsules.

Solid compositions for oral administration include tablets, granulates and capsules. In any case the manufacturing process is based on a simple mixture, dry or wet granulation of the active ingredient with excipients. These excipients can be, for example, diluents such as lactose, microcrystalline cellulose, mannitol or calcium hydrogenphosphate; binding agents such as for example starch, gelatin or polyvinylpyrrolidone; disintegrants such as sodium carboxymethyl starch or

sodium croscarmellose; and lubricating agents, such as for example magnesium stearate, stearic acid or talc. Tablets can be additionally coated with suitable excipients by known techniques for the purpose of delaying their disintegration and absorption in the gastrointestinal tract, and thereby provide a sustained action over a longer period or simply to improve their organoleptic properties or their stability. The active ingredient can be also incorporated by coating on inert *pellets* using natural or synthetic filmogenic polymers. Soft gelatin capsules are also possible, wherein the active ingredient is mixed with water or an oily medium, for example coconut oil, liquid paraffin, or olive oil.

Powders and granulates for the preparation of oral suspensions by the addition of water can be obtained by mixing the active ingredient with dispersing or wetting agents; suspending agents and preservatives. Other excipients can also be added, for example sweetening, flavoring and coloring agents.

Liquid forms for oral administration include emulsions, solutions, suspensions, syrups and elixirs containing commonly-used inert diluents, such as distilled water, ethanol, sorbitol, glycerol, polyethylene glycols and propylene glycols. Said compositions can also contain coadjuvants such as wetting, suspending, sweetening, flavoring, preserving agents and buffers.

Injectable preparations, according to the present invention, for parenteral administration, comprise sterile solutions, suspensions or emulsions, in an aqueous or non-aqueous solvent such as propylene glycol, polyethylene glycol or vegetable oils. These compositions can also contain coadjuvants, such as wetting, preserving, emulsifying and dispersing agents. They may be sterilized by any known method or prepared as sterile solid compositions to be dissolved in water or any other sterile injectable medium immediately before use. It is also possible to start from sterile materials and keep them under these conditions throughout all the manufacturing process.

For the rectal administration, the active ingredient can be formulated preferably as a suppository on an oily base, such as for example vegetable oils or solid semisynthetic glycerides, or on a hydrophilic base such as polyethylene glycols.

The following examples illustrate the present invention and are not to be understood as limiting the scope of the invention in any way. The following abbreviations have been used in the examples:

Ac_2O: acetic anhydride

AcOH: acetic acid

DMF: dimethylformamide

EtOAc: ethyl acetate

MeOH: methanol

Example 1: Methyl 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoate

a) 2,2,3,3,3-Pentafluoropropyl tosylate

To a solution of 2,2,3,3,3-pentafluoropropanol (5.0 mL, 50 mmol) and pyridine (8.1 mL, 100 mmol) in chloroform (100 mL), cooled at 0 °C and under argon, tosyl chloride (14.29 g, 75 mmol) was slowly added. The resulting mixture was allowed to warm to room temperature and it was stirred at this temperature overnight. Then a 10% K_2CO_3 solution in water was added and the mixture was vigorously stirred for 30 min. The layers were separated, and the organic layer was treated again with K_2CO_3. After that, it was washed with 2 N HCl, dried over Na_2SO_4 and then concentrated to dryness, yielding 12.72 g of the desired compound (84% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 2.47 (s, 3 H), 4.41 (t, J = 12.3 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H).

b) Title compound

A mixture of methyl 2,4-dihydroxybenzoate (5.04 g, 30 mmol) and K_2CO_3 (4.56 g, 33 mmol) in DMF (30 mL) was heated under argon at 50 °C for several minutes. It was cooled to room temperature, 2,2,3,3,3-pentafluoropropyl tosylate (10.03 g, 33 mmol), obtained in the preceding section, was added and the resulting mixture was stirred at 50 °C overnight, at 80 °C for 6 hours and finally at 50 °C for 3 days. It was allowed to cool to room temperature and it was acidified by the addition of 6 N HCl. The mixture obtained was extracted with EtOAc (x4), the combined organic layers were washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was purified by chromatography on silica-gel using hexane-EtOAc mixtures of increasing polarity as eluent, yielding the title compound of the example as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 3.94 (s, 3 H), 4.43 (t, J = 12.1 Hz, 2H), 6.49 (complex signal, 2 H), 7.79 (d, J = 8.5 Hz, 1 H), 10.99 (s, 1 H).

Following a similar procedure to that described in steps a and b of example 1, but starting in each case from a suitable alcohol for the preparation of the corresponding intermediate of step a, the following compounds were obtained:

Example 2: Methyl 2-hydroxy-4-(2,2,2-trifluoroethoxy)benzoate

Starting alcohol: 2,2,2-trifluoroethanol

M_p = 78 – 79 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 3.94 (s, 3H), 4.38 (q, J = 8.0 Hz, 2H), 6.50 (complex signal, 2 H), 7.81 (d, J = 8.8 Hz, 1 H), 11.00 (s, 1 H).

Example 3: Methyl 2-hydroxy-4-(2,2,3,3-tetrafluoropropoxy)benzoate

Starting alcohol: 2,2,3,3-tetrafluoropropanol

M_p = 224 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 3.93 (s, 3 H), 4.39 (t, J = 10.4 Hz, 2H), 6.04 (tt, J_{gem} = 53.1 Hz, J_{vic} = 4.7 Hz, 1 H), 6.48 (complex signal, 2 H), 7.79 (d, J = 9.5 Hz, 1 H), 10.98 (s, 1 H).

Example 4: Methyl 2-hydroxy-4-(2-fluoroethoxy)benzoate

Starting alcohol: 2-fluoroethanol

M_p = 64 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 3.98 (s, 3 H), 4.29 (d of m, J_{H-F} = 27.7 Hz, 2 H), 4.82 (d of m, J_{H-F} = 47.3 Hz, 2H), 6.51 (s, 1 H), 6.53 (d, J = 8.7 Hz, 1 H), 7.81 (d, J = 8.7 Hz, 1 H), 11.04 (s, 1 H).

Example 5: Methyl 4-(2,2-difluoroethoxy)-2-hydroxybenzoate

Starting alcohol: 2,2-difluoroethanol

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 3.93 (s, 3 H), 4.19 (td, J_{H-F} = 12.9 Hz, J_{H-H} = 4.1 Hz, 2 H), 6.09 (tt, J_{H-F} = 54.9 Hz, J_{H-H} = 4.1 Hz, 1H), 6.47 (complex signal, 2 H), 7.77 (d, J = 8.9 Hz, 1 H), 10.98 (s, 1 H).

Example 6: 2-Hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid

Method A:

a) 2,2,3,3,3-Pentafluoropropyl trifluoromethanesulfonate

A mixture of trifluoromethanesulfonic anhydride (40 mL, 0.24 mol) and 2,2,3,3,3-pentafluoropropanol (25 mL, 0.24 mol) was heated under argon at 90 °C overnight. Then, the mixture was distilled under atmospheric pressure yielding the desired product as a colorless oil (97% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ (TMS): 4.78 (t, J = 11.7 Hz, 2 H).

b) Title compound

To a mixture of 95% NaH (1.43 g, 56.64 mmol) in DMF (12 mL) under argon, a solution of 2,4-dihydroxybenzoic acid (3.00 g, 18.88 mmol) in DMF (18 mL) was added and the resulting suspension was stirred at room temperature for 30 min. $B(OCH_3)_3$ (6.3 mL, 56.64 mmol) was added dropwise and the reaction mixture was stirred for one additional hour at room temperature. Then, the compound obtained in the preceding section (5.0 mL, 28.32 mmol) was added dropwise and the resulting mixture was stirred at 100 °C overnight. It was cooled to room temperature and acidified to pH 1 by the addition of 1 N HCl. The solution obtained was extracted with EtOAc and the organic layer was washed with H_2O and brine. It was dried over Na_2SO_4 and concentrated to dryness. The crude product obtained was recrystallized in AcOH (4 times, 3 mL AcOH each time) yielding the title compound of the example as a slightly colored solid (66% yield).

M_p = 147 –148 °C

^{1}H NMR (200 MHz, $CDCl_3$) δ (TMS): 4.42 (t, J = 12.4 Hz, 2H), 6.45 (d, J = 2.2 Hz, 1 H), 6.50 (d, J = 2.6 Hz, 1 H), 7.82 (d, J = 8.4 Hz, 1 H).

Method B:

To a solution of methyl 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoate (obtained in example 1) (0.72 g, 2.40 mmol) in MeOH (9.7 mL), KOH (0.51 g, 86 %; 7.80 mmol) dissolved in H_2O (3 mL) was added and the resulting mixture was refluxed for 4 hours. It was allowed to cool and MeOH was evaporated. The residue obtained was treated with H_2O (5 mL) and the resulting solution was acidified by the addition of 6 N HCl. The white solid

formed was collected by filtration, washed with cold H_2O and dried *in vacuo*, yielding the title compound of the example (55% yield).

Following a similar procedure to that described in method B of example 6, and starting in each case from the suitable ester, the following compounds were obtained:

Example 7: 2-Hydroxy-4-(2,2,2-trifluoroethoxy)benzoic acid

Starting ester: methyl 2-hydroxy-4-(2,2,2-trifluoroethoxy)benzoate (obtained in example 2)

M_p = 177 – 179 °C

^{1}H NMR (300 MHz, CD_3OD) δ (TMS): 4.63 (q, J = 8.4 Hz, 2H), 6.61 (complex signal, 2 H), 7.87 (d, J = 8.1 Hz, 1 H).

Example 8: 2-Hydroxy-4-(2,2,3,3-tetrafluoropropoxy)benzoic acid

Starting ester: methyl 2-hydroxy-4-(2,2,3,3-tetrafluoropropoxy)benzoate (obtained in example 3)

M_p = 145 – 151 °C

^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ (TMS): 4.39 (t, J = 12.1 Hz, 2H), 6.12 (tt, J_{gem} = 52.8 Hz, J_{vic} = 4.9 Hz, 1 H), 6.47 (complex signal, 2 H), 7.80 (d, J = 8.6 Hz, 1 H).

Example 9: 2-Hydroxy-4-(2-fluoroethoxy)benzoic acid

Starting ester: methyl 2-hydroxy-4-(2-fluoroethoxy)benzoate (obtained in example 4)

M_p = 160 °C

^{1}H NMR (300 MHz, CD_3OD) δ (TMS): 4.22 (d of m, J_{H-F} = 28.8 Hz, 2 H), 4.71 (d of m, J_{H-F} = 47.7 Hz, 2H), 6.47 (complex signal, 2 H), 7.76 (d, J = 8.7 Hz, 1 H).

Example 10: 4-(2,2-Difluoroethoxy)-2-hydroxybenzoic acid

Starting ester: methyl 4-(2,2-difluoroethoxy)-2-hydroxybenzoate

M_p = 154 – 163 °C

^{1}H NMR (300 MHz, CD_3OD) δ (TMS): 4.31 (td, J_{H-F} = 13.7 Hz, J_{H-H} = 3.8 Hz, 2 H), 6.22 (tt, J_{H-F} = 54.8 Hz, J_{H-H} = 3.8 Hz, 1H), 6.55 (complex signal, 2 H), 7.84 (d, J = 8.6 Hz, 1 H).

Example 11: 2-Acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid

A solution of 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid (obtained in example 6) (0.45 g, 1.6 mmol) in 3 mL of pyridine was cooled to 0 °C and Ac_2O (0.25 mL) was added. The resulting mixture was stirred for 15 min at 0°C and for 2 h at room temperature. It was concentrated and the residue was treated with H_2O (10 mL) and stirred until precipitation (2 h). It was filtered, and the solid obtained was purified by chromatography on silica-gel using hexane-EtOAc mixtures of increasing polarity as eluent yielding 0.2 g of the desired product as a white solid (38 % yield).

M_p = 126 °C

^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$) δ (TMS): 2.29 (s, 3 H), 4.52 (t, J = 12.7 Hz, 2 H), 6.70 (d, J = 2.5 Hz, 1 H), 6.90 (d, J = 8.8 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 1 H).

Example 12: 2-Acetoxy-4-(2-fluoroethoxy)benzoic acid

Following a similar procedure to that described in example 11, but using 2-hydroxy-4-(2-fluoroethoxy)benzoic acid (obtained in example 9) instead of 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid, the title compound of the example was obtained.

M_p = 126 - 127 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ (TMS): 2.34 (s, 3 H), 4.28 (d, J = 25.1 Hz, 2 H), 4.77 (d, J = 47.3 Hz, 2 H), 6.67 (d, J = 2.5 Hz, 1 H), 6.87 (d, J = 8.9 Hz, 1 H), 8.09 (d, J = 8.9 Hz, 1 H).

The utility of the compounds of the present invention for the treatment of psoriasis and other immune diseases can be shown using the following pharmacological tests:

Test 1- Oxazolone-induced delayed hypersensitivity in mice

Method: Male Swiss mice (25-30 g body weight) were sensitized by the application of a 2% solution of oxazolone (Sigma) in acetone (50 μL) into the shaved abdomen of the animals. Seven days later, 25 μL of a 1.5% solution of oxazolone was applied on both surfaces of the right ear. The left ear served as a sham and was only treated with the vehicle (acetone). 20 μL of the test compound (dissolved in acetone) or of vehicle alone (control) was applied on both sides of the right ear, 24 h before challenge and 1 and 5 h after challenge. To evaluate the edema, the mice were killed (by CO_2 inhalation) and an 8 mm disc was excised from the right and left ears. The edema was measured by the difference in weight between the two ears and expressed as a percentage in relation to the control group.

Results: The results obtained with the compound of example 6 are shown in figure 1. It can be observed that this compound produced a concentration-dependent inhibition of the edema. Similar results are obtained when the product of example 6 is administered as an ointment (obtained by dissolving the product in diethylene glycol monoethyl ether and incorporating this into the base excipient YR-2446®) instead of dissolved in acetone.

Test 2- Psoriasis model in immune-deficient BNX mice transplanted with human psoriatic skin

Method: The goal of this study is to assess the effect of the test compounds on the development of a psoriatic lesion induced by super-antigen-activated human peripheral blood T-cells, in non-lesional skin from a psoriasis patient transplanted onto an immune-deficient BNX mouse. Mice (male/female, circa 20 g, 5 mice per group) were transplanted with a non-lesional skin graft from psoriasis patients. Peripheral blood mononuclear cells from the same patients were also isolated and stored in freezer until further use. Transplants were allowed to “take” for 4 weeks. After this period, transplants were treated topically with the test compound or vehicle (control) for 1 week. Then the lesion was induced by the intra-dermal injection of peripheral blood mononuclear cells from psoriatic patients, previously activated *in vitro* for 2 days with super-antigen. The treatment was continued with the test compound or vehicle for two additional weeks. Transplants were then

harvested and epidermal thickness was measured by using computer-aided morphometric analysis.

Results: The compound of example 6, administered as an ointment (obtained as described in test 1) at the concentration of 0.1%, produced a significant inhibition ($p < 0.01$) of the increase of the epidermal thickness induced by intradermal injection of activated mononuclear cells.

Test 3- Inhibition of adjuvant-induced arthritis in the rat

Method: Male Lewis rats with body weight between 140 and 170 g and 7 week-old were used. Before the start of the study animals were acclimated for a period of at least 5 days. Animals were fasted for 18 hours before their use, with water *ad libitum*. Throughout the study, animals were allowed free access to drinking water, except during observation periods.

Groups of five animals were randomized (Sham, Control and Test compound). The duration of the protocol was 28 days. Arthritis was induced on day 1 of the study by a single subplantar injection of 0.1 mL of an emulsion prepared with 10 mg of *Mycobacterium butyricum* and 10 mL of Freund's incomplete adjuvant (Difco) to the right hindpaw of the animals from the Control (C) and Test compound (T) groups. Sham animals (S) received 0.1 mL of Freund's incomplete adjuvant. The test compound was administered daily from day 1 of the study until day 28 at a dose of 10 mg/kg p.o. as a suspension in Tween 80® (1%), while the Control group only received the vehicle. On day 28 of the development of arthritis, the volume of the left paw (secondary edema) was determined using a UGO BASILE 7150 plethysmometer.

The inhibition of the increase in volume was calculated as follows:

$$\% \text{ Inh.} = 100 - ((T-S)/(C-S)) * 100$$

Where: T = Test compound group; C = Control group; and S = Sham group

Results: Oral administration of the compound of example 6 for 28 days at the dose of 10 mg/kg/day produced a significant inhibition of the paw volume increase of immunological origin induced by *M. butyricum* and adjuvant in control animals.

Test 4 – Immunosupression model: murine mixed lymphocyte reaction

Method: Immunosuppression was determined by testing the effects of the compounds on the proliferation of splenic lymphocytes from C57BL/6 mice strain stimulated with splenic lymphocytes from CBA mice strain. Splenic lymphocytes were isolated from CBA (acting as stimulating cells) and C57BL/6 mice strains (acting as proliferating cells). Homogenized mouse spleen was filtered and subsequently centrifuged at 250 x g for 5 minutes at 4 °C. The *pellets* were resuspended in culture medium (RPMI 1640 supplemented with 5% fetal calf serum and 2% antibiotics) and after repeating this process twice they were adjusted to a final density of $5x10^6$ cells/mL. The isolated lymphocytes from CBA strain were treated with mitomycine C to block their proliferation.

In a 96-well plate the various dilutions of the test compounds or culture medium (for the control) were distributed. Next, $5x10^5$ C57BL/6 cells and $2.5x10^5$ CBA cells were added and incubated for 48 h (37 °C, 5% CO_2). After this preincubation 1 μCi of [^{3}H]-thymidine and 0.2 mM of unlabeled thymidine were added to each well and the mixture was incubated or another 24 h. At the end of this period, the samples were transferred into a filter plate (Millipore) and the cells were washed 3 times with phosphate-buffered saline solution.

Lymphocyte proliferation was measured as [^{3}H]-thymidine incorporation into the DNA of proliferating cells (C57BL/6) by a liquid scintillation counter (LS series, Beckman).

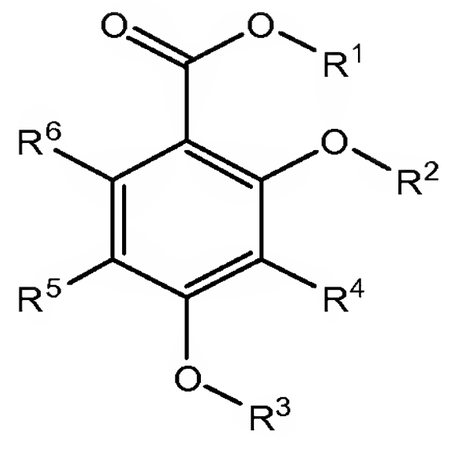
Results: The compound of example 6 at a concentration of 300 μM inhibited completely mice splenic lymphocyte proliferation. When administered at 100 μM, it gave 60% inhibition of the proliferation.

Similar results were obtained with the compound of example 6 in a human T-lymphocyte proliferation inhibition assay.

The results of the preceding tests with a representative compound of the invention demonstrate the utility of the compounds of formula **I** in the treatment or prevention of psoriasis and other immune diseases, such as those mentioned above.

CLAIMS

1.- A compound of general formula **I**:



I

wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or -C(=O)R^7;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, -NR^8R^9, -$S(O)_xR^{10}$ or -C(=O)R^{11};

R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

with the proviso that when R^1 represents methyl, R^2 represents hydrogen, R^3 represents 1,1,2,2-tetrafluoroethyl and R^4 and R^5 represent hydrogen then R^6 cannot be hydroxy, and with the further proviso that when R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents 3-fluoropropyl then R^4, R^5 and R^6 together cannot simultaneously represent fluoro;

and the salts, solvates and prodrugs thereof.

2.- A compound according to claim 1 wherein R^4, R^5 and R^6 represent hydrogen.

3.- A compound according to claim 1 or 2 wherein R^3 represents a C_{1-5} fluoroalkyl group.

4.- A compound according to claim 1 or 2 wherein R^3 represents a C_{1-3} fluoroalkyl, C_{2-3} fluoroalkenyl or C_{2-3} fluoroalkynyl group.

5.- A compound according to claim 1 or 2 wherein R^3 represents a C_{1-3} fluoroalkyl group.

6.- A compound according to claim 1 or 2 wherein R^3 represents a 2,2,3,3,3-pentafluoropropyl group.

7.- A compound according to any of claims 1 to 6 wherein R^1 represents hydrogen.

8.- A compound according to any of claims 1 to 7 wherein R^2 represents hydrogen or acetyl.

9.- A compound according to claim 1 selected from:

methyl 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoate;

methyl 2-hydroxy-4-(2,2,2-trifluoroethoxy)benzoate;

methyl 2-hydroxy-4-(2,2,3,3-tetrafluoropropoxy)benzoate;

methyl 2-hydroxy-4-(2-fluoroethoxy)benzoate;

methyl 4-(2,2-difluoroethoxy)-2-hydroxybenzoate;

2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid;

2-hydroxy-4-(2,2,2-trifluoroethoxy)benzoic acid;

2-hydroxy-4-(2,2,3,3-tetrafluoropropoxy)benzoic acid;

2-hydroxy-4-(2-fluoroethoxy)benzoic acid;

4-(2,2-difluoroethoxy)-2-hydroxybenzoic acid;

2-acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid; and

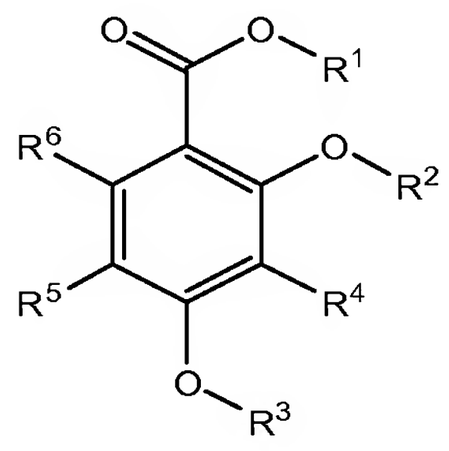
2-acetoxy-4-(2-fluoroethoxy)benzoic acid;

or a salt, solvate or prodrug thereof.

10.- 2-Hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid and the salts, solvates and prodrugs thereof.

11.- 2-Acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid and the salts, solvates and prodrugs thereof.

12.- A compound of general formula **I**:



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wherein:

R^1 represents hydrogen or C_{1-4} alkyl;

R^2 represents hydrogen or $-C(=O)R^7$;

R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

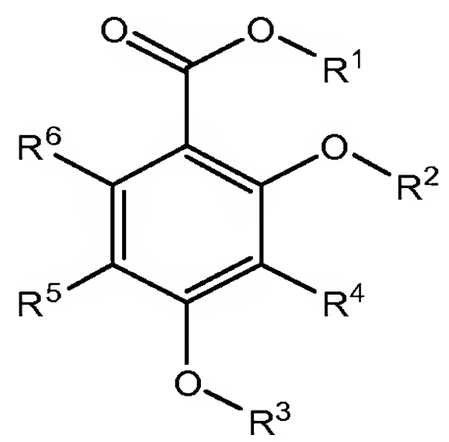
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a salt, solvate or prodrug thereof, for use as an active pharmaceutical ingredient.

13.- A compound of general formula **I**:



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R^3 represents a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, $-NR^8R^9$, $-S(O)_xR^{10}$ or $-C(=O)R^{11}$;

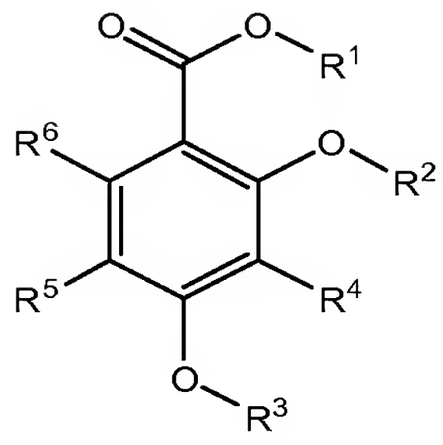
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a salt, solvate or prodrug thereof, for use in a method of treatment of the human or animal body.

14.- A pharmaceutical composition which comprises an effective amount of a compound of formula **I**



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R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, -NR^8R^9, -$S(O)_xR^{10}$ or -C(=O)R^{11};

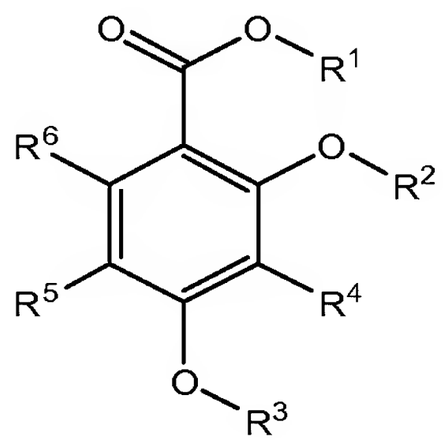
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a pharmaceutically acceptable salt, solvate or prodrug thereof and one or more pharmaceutically acceptable excipients.

15.- Use of a compound of formula **I**



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R^3 represents C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl;

R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, -NR^8R^9, -$S(O)_xR^{10}$ or

-C(=O)R^{11};

R^7 and R^{10} independently represent C_{1-4} alkyl;

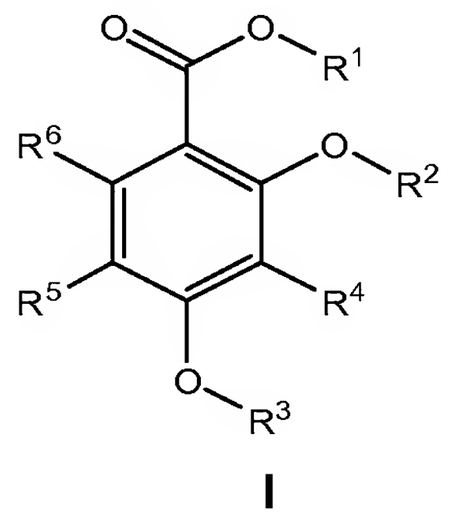
R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

or a pharmaceutically acceptable salt, solvate or prodrug thereof for the manufacture of a medicament for the treatment or prevention of immune diseases.

16.- Use according to claim 15 wherein the immune disease is selected from among psoriasis, other skin diseases such as atopic dermatitis, contact dermatitis, lichen planus, dermatomyositis, scleroderma, erythema multiforme, urticaria and pemphigus, inflammatory bowel disease including Crohn's disease and ulcerative colitis, rheumatoid arthritis and other arthritic diseases such as gouty arthritis, psoriatic arthritis, juvenile arthritis and ankylosing spondylitis, multiple sclerosis and other autoimmune neuropathies, diabetes, transplant rejection, graft-versus-host disease, lupus erythematosus, vasculitis, Sjögren's syndrome, Guillain-Barre syndrome, glomerulonephritis, respiratory diseases such as allergic rhinitis or asthma, and neoplasias with immune system cell proliferation.

17.- Process for preparing a compound of formula **I**,



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R^4, R^5 and R^6 independently represent hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, halogen, cyano, hydroxy, nitro, -NR^8R^9, -$S(O)_xR^{10}$ or -C(=O)R^{11};

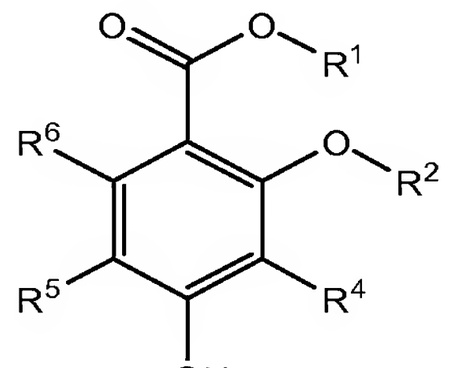
R^7 and R^{10} independently represent C_{1-4} alkyl;

R^8, R^9 and R^{11} independently represent hydrogen or C_{1-4} alkyl; and

x represents 0, 1 or 2;

which comprises:

(a) reacting a phenol of formula **II**



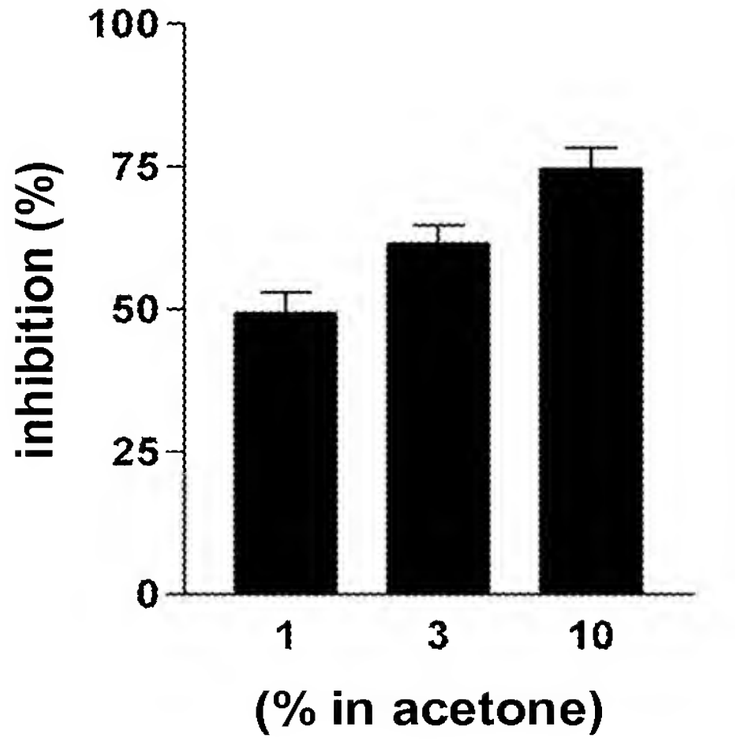
II

wherein R^1, R^2, R^4, R^5 and R^6 have the meaning described above, with an alkylating agent of formula G-R^3 (**III**), wherein R^3 has the meaning described above and G represents a good leaving group; or

(b) converting, in one or more steps, a compound of formula **I** into another compound of formula **I**; and

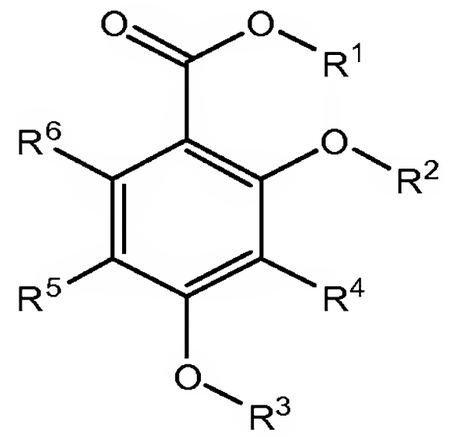
(c) if desired, after the above steps and when R^1 and/or R^2 represent hydrogen, reacting a compound of formula **I** with a base, yielding the corresponding addition salt.

Figure 1



ABSTRACT

The present invention relates to novel compounds of formula **I** and to the salts, solvates and prodrugs thereof, wherein the meanings of the various substituents are as disclosed in the description. Said compounds are useful for the treatment of psoriasis and other immune diseases.



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